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*A Contribution to Our Knowledge of  
Epidemic Cerebro-Spinal Meningitis.*

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A CONTRIBUTION TO OUR KNOWLEDGE OF EPIDEMIC  
CEREBRO-SPINAL MENINGITIS.<sup>1</sup>

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EPIDEMIOLOGY, ETIOLOGY, AND PATHOLOGY.

THE epidemic of cerebro-spinal meningitis to be reported here was one of the most extensive which has prevailed either in this country or abroad for many years. The outbreak, which began in January, had by the first of February become so alarming as to lead the State Board of Health to decide on making an official investigation for the purpose of determining the cause, and, if possible, of adopting some means to prevent the further spread of the disease.

The fact that one of us (Dr. Flexner) was officially delegated to make this investigation made it easy for us to gain access to a large number of cases, and we wish to acknowledge gratefully the many kindnesses, direct and indirect, received at the hands of Dr. C. W. Chancellor, Secretary of the State Board; Drs. J. D. and W. Q. Skilling, Drs. M. G. and A. S. Porter, Dr. J. O. Bullock, of Lonaconing, and Dr. A. W. Smith, of Ocean. Without the co-operation of these gentlemen these researches would have been impossible; as it was, every opportunity was given us for a full and complete study of all individuals affected during our visit to the diseased region.

The town of Lonaconing is a mining centre in the Alleghany mountains and contains some 5000 inhabitants. The location is peculiar and is more or less of interest from an epidemiological standpoint. The town is situated in a narrow valley and extends well up the sides of the steep hills which enclose it. Through the bottom of the gulch runs a muddy stream known as George's Creek. The mountains rise more or less abruptly from the edges of the creek, and the town may, for our purpose, be divided into two parts: first, that lying in the valley in

<sup>1</sup> A report on the epidemic disease which prevailed during the winter and spring of 1893 at Lonaconing, Maryland, and at other places in the George's Creek valley.





which are situated the business portion and for the most part the dwellings of the professional and business men of the place, and second, that built on the mountain sides, consisting almost entirely of miners' dwellings. The stream and valley are somewhat tortuous at this spot, and give the place the appearance of being surrounded on all sides by mountains.

One is struck almost at once by the arrangement of the houses on the incline. They are placed in long rows, tier above tier, facing the valley; behind, and therefore above the houses, are situated the privies, placed flat upon the ground; and not infrequently the cow-stable is located quite close to the dwelling. Before our arrival at Lonaconing there had been a heavy snowfall, but the weather soon afterward became mild, the snow melted, and exposed to view and made doubly striking by contrast the dreadful conditions which existed. The water streamed down the mountain sides, carrying with it the general refuse from the yards, the material from the cow-stables, and the excreta from the outhouses of the upper tiers, through the yards, past the dwellings situated below, and finally entered the creek, which acts as a huge sewer winding through the centre of the town. On their way these polluted surface-washings found no system of drains for their reception, and in places crossed the common roadway in little rivulets, through which the inhabitants of the town had to drive and walk.

The water supply of Lonaconing is derived partly from surface wells and partly from cisterns, and we actually observed during a thaw the entrance of surface water and the accompanying filth directly into wells which were in daily use for drinking and culinary purposes. Significant, too, is the fact that in the valley the wells are situated often only a few feet from the creek, and it is certainly not hard to believe that the contaminated water from the creek could penetrate through the soil and become mixed with the water of the wells. The slaughter-houses are in the heart of the town upon the banks of the creek, and the blood and waste material from these find their way into its waters.

These unsanitary conditions are not confined to Lonaconing alone, but in its course George's Creek passes through a number of small towns, each of which adds its quota to the general filth, and only a short time ago an investigating party inspecting the river between Westernport and the Phoenix mines found among other things carcasses of horses in the stream or lying along the banks.

The population of Lonaconing is chiefly made up of coal-miners and their families. In many instances there was distinct evidence of overcrowding, as many as eight and ten individuals living, eating and sleeping in a house of four small rooms. In one house in which a fatal

case occurred eleven persons slept in three bed-rooms. The individual houses in the long rows on the hillside are built so close to one another that often there is scarcely room for a footpath between them. There were, however, among them many well-built and commodious houses, though, as we shall show later, the occupants of these were by no means immune from the disease.

From what we have said it will be obvious that, whether or not cerebro spinal meningitis is a filth disease, Lonaconing and the other towns situated along the banks of George's Creek are, and have been for years, in about as unsanitary a condition as could be well imagined, and it would be little wonder if typhoid fever, diphtheria, dysentery, and the whole group of filth diseases should find in them an endemic home. And during the past spring, besides meningitis, the medical men of Lonaconing have had under their care many cases of scarlet fever, measles, parotitis (an epidemic of over 100 cases), influenza, pneumonia, diphtheria, and acute articular rheumatism.

By far the greater number of the cases of meningitis occurred in the higher portions of the town, and they were usually found confined to little foci or groups of houses, points which have been noted by different observers also in other epidemics. To this rule, however, there were numerous exceptions. A few of the patients lived close upon the margin of the creek, and isolated cases were by no means rare. One boy, who died on the ninth day of the disease, lived on Jackson Hill, fully a quarter of a mile from any other habitation, and of the patients at Ocean none lived more than thirty feet above the level of the stream.

The earliest cases of which we have notes occurred during the first week in January, 1893. During the course of a dance two young men who had overheated themselves imprudently rushed into the open air to get cool. The weather outside was extremely cold, and it is said that their hair, wet with perspiration, was frozen upon their heads. The drive to their homes afterward was long and very cold, and these two men, aged twenty and twenty-two respectively, developed symptoms of cerebro spinal meningitis next day. Immediately afterward the disease became epidemic, appearing in many different places in Ocean, Midland and Lonaconing about the same time. After every marked fall of temperature there were fresh cases to record, and the disease prevailed there in varying intensity up to the middle of May. Up to March 1st there had been sixty-eight well-marked cases, besides some forty which were classed as abortive cases, making a total of over one hundred cases. Since our return there have been many more cases in Lonaconing, as well as an alarming outbreak in Frostburg, making the total number of cases about 200.

Of the sixty-eight patients in whom the symptoms were clearly defined thirty-seven were males and thirty-one females. In other epidemics the



number of females attacked had, as a rule, slightly exceeded that of the males, and it would seem probable, therefore, that sex bears little or no relation to the etiology of the disease. Undoubtedly, children and young adults were most susceptible, although the occurrence of the disease among older people cannot be denied, one of our cases being a man of thirty-eight years, another a woman of forty. The youngest patient observed was a child of five months.

The study of different epidemics of cerebro-spinal meningitis has not as yet led to the detection of a common factor or set of conditions in the localities attacked. The disease shows no special predilection, so far as one can judge, for particular regions, or for any season of the year, and no one class of people is affected, the apparently robust and the weak suffering alike. It has, indeed, been established that, *cæteris paribus*, young individuals are more susceptible than adults, and although there is no sharp line to be drawn in the occurrence of the disease under different circumstances, yet its greater frequency under unfavorable hygienic surroundings, such for example as in barracks and in country districts, is to be borne in mind. Epidemics have occurred in the same district, affecting areas slightly removed from one another. Such an epidemic, studied by Low, appeared in 1890 in certain of the eastern counties of England. The parishes affected all lay within short distances of one another in agricultural communities, in all of which it was the custom to use the house-refuse for fertilizing purposes. The drinking-water was obtained from wells and from open pits, though the water from the latter is said to have been boiled before being used. In other epidemics, after a considerable period of quiescence, the disease has reappeared in the same locality, examples of which are given by Wolff, who studied the Hamburg epidemic.

Osler states that epidemics have occurred more frequently in winter and spring, and that villages and country places have in certain of these suffered relatively more than cities. The Leipzig epidemic which Strümpell studied appeared there in 1879, continued into 1880 and 1881, beginning in the winter and becoming more severe in April and June, almost ceasing in February and March of 1881, only to appear again in a sporadic form later. Clavierie described an epidemic at Rochefort which prevailed during the winter of 1885-86 in which there were marked oscillations of temperature, although at no time did the thermometer fall below zero. Lemoine observed in the epidemic at Orleans during the winter of 1886 that a sudden lowering of the temperature was followed in one or two days by a marked increase in the number of cases.

The epidemic at Lonaconing appeared in the winter and reached its maximum during the coldest weather. The winter was, moreover, one remarkable for its severity, and there were heavy falls of

snow, with very cold weather alternating with thaws of short duration. During the month of February, however, when the cases were perhaps most numerous, the weather, as shown by the observations reported from Cumberland, Md., to the U. S. Weather Bureau, was exceptional only for the rainfall, for while the average rainfall for the month of February during the past twenty-two years has been 2.51 inches, this year the rain and melted snow amounted to 3.58 inches, the snowfall itself measuring twenty inches. During the month there were eight clear days, two cloudy, ten fair, and eight of rain and snow. The highest temperature during February, 1893, was 58° F., the lowest 3° F.; mean 33° F. The averages for the last twenty-two years are: Highest temperatures 58°, lowest 2°; mean temperatures, 33°. It may be mentioned that this epidemic agrees with that described by Low in that the disease occurred in several of the neighboring places in the same valley.

The epidemic and sporadic cases of cerebro-spinal meningitis which have occurred since 1886 are of especial interest inasmuch as they have been studied bacteriologically. This method of study has been rewarded by the isolation of a particular micro-organism from the exudate in the meninges, namely, the micrococcus lanceolatus, which there is now reason to believe bears an etiological relation to the disease.

Weichselbaum found this organism in the exudate in the meninges in 1886, and Netter obtained it from cases in the epidemic studied by Lemoine in the same year. Goldschmidt isolated it from a case in 1887, Ortmann in 1888, and Foà and Bordoni-Uffreduzzi in cases in an epidemic occurring in Turin in 1888. Banti found it in 1889, and Bonome obtained it at autopsies during a small epidemic in Padua, which occurred in 1890. Mirto obtained the micrococcus lanceolatus in 1891 from the exudate in a case of epidemic cerebro-spinal meningitis—a man twenty-two years of age. The cocci were in every way typical, and when inoculated into rabbits gave rise to fatal septicæmia. Klippel found it in sporadic cases in 1891 and Ribbert in 1892. Ribbert's cases were those of two brothers who were affected almost simultaneously, one of them dying in forty-three, the other in forty-seven hours.

The first to isolate the micrococcus lanceolatus from the exudate in meningitis was Eberth, in 1880. The meningitis in this case was secondary to pneumonia. Since this time many others have studied this form of meningitis and have obtained the same organism. Thus Bozzolo and Leyden in 1883, Weichselbaum and Fraenkel in 1886, and Meyer and Netter in 1887; Hansen and Bonome in 1888, Monti in 1889, and Gabbi and Puritz in 1890. In Professor Welch's laboratory in Baltimore, in three cases recently the same organism was isolated.

There is another class of cases in which a meningitis develops in the course of diseases other than pneumonia, or follows upon injuries. In some of these the micrococcus lanceolatus has been found, in others dif-



ferent bacteria. For example, Netter found in 1889 the Friedländer bacillus in a case of meningitis following otitis media. Mills claims to have isolated the Friedländer bacillus also from a case of pneumonia associated with meningitis, but it is not improbable that his organism was the Fraenkel-Weichselbaum diplococcus. Monti, in the same year, found the micrococcus lanceolatus in a case of combined arthritis and pleuritis. Kainen, in 1890, separated a bacillus which he regarded as identical with the typhoid bacillus; and in the previous year Adenot had likewise isolated an organism which he thought to be the typhoid bacillus. Debove about this time described a case of combined peritonitis and meningitis due to the pneumococcus. Hanot and Luzet, in 1890, isolated streptococci from the exudate in the meninges in a puerperal woman who had died of meningitis and general infection. Le Gendre and Beaussenat, in 1892, obtained from a case of meningitis associated with otitis media, arthritis, and broncho-pneumonia, the staphylococcus pyogenes aureus. Klippel, in 1892, found, in a demented individual who died of acute meningitis, the micrococcus lanceolatus. There was an old area of softening present, and over this the exudate was most marked. Boulay and Courtois-Suffit, in 1890, isolated the micrococcus lanceolatus from a case of combined peritonitis and meningitis without pneumonia, and Bonome has observed a case of combined pleuritis, pericarditis and meningitis due to the pneumococcus. Zorkendorfer, writing from Chiari's laboratory, reports a very interesting case observed during this year in which at autopsy, besides a purulent meningitis, there was a well-marked inflammation in the ethmoid cavity and suppuration in the sphenoidal sinuses. Besides, the mucous membrane of the pharynx was reddened and covered with a thin layer of pus. From the pus in the meninges, as well as that in the sphenoidal sinuses, he found diplococci in cover-slips. He succeeded in isolating them also in pure culture, and found, by injection into the peritoneal cavity of rabbits, that they set up a fatal septicæmia, the organisms in the blood at autopsy corresponding in every respect to the micrococcus lanceolatus. In three cases of purulent meningitis examined by Neumann and Schaeffer, once the pneumococcus, once the staphylococcus pyogenes aureus, and in the remaining instance a fine bacillus was found. In a fourth case the results of the examination were negative. Netter has also in one case found the staphylococcus pyogenes aureus. Roux states that he isolated from a case the staphylococcus aureus and albus and a bacillus resembling that of typhoid fever. Mircoli claims to have obtained from one case a staphylococcus resembling the aureus and a bacillus which he identified as the bacillus pyogenes fœtidus, the latter being obtained in cultures from the motor cortex and medulla.

Früs describes an epidemic at Copenhagen in which 185 persons (111 under fifteen years of age) were affected. From the pus of nine cases



examined by Roosing a thick, short bacillus was obtained which is described as approaching a coccus in form, and is stated to grow characteristically on gelatin. We recently made an autopsy on a young man who died of meningitis, following an injury to the head. There was contusion of the scalp but no loss of continuity in the bones of the skull. In the exudate of the meninges the micrococcus lanceolatus was found; no other focus of suppuration was present in the body. Prudden, in a case of traumatic meningitis occurring in a child of thirteen months (a patient of Holt's) has isolated the micrococcus lanceolatus from the exudate. White mice inoculated with the organism died in thirty-six hours from septicæmia.

The number of bacteriological examinations of uncomplicated cases of meningitis, occurring either sporadically or in epidemic form, is up to the present time not large. There is, however, such uniformity in the results obtained that while it is perhaps not to be considered as established for all, yet the majority of cases appear to be caused by an organism which, in its morphological characters and biological properties, is not to be distinguished from the micrococcus lanceolatus.

During our stay at Lonaconing two deaths occurred, and we were permitted to make autopsies. The first was a child of nine years, who died on the third day of the disease. The autopsy showed an extensive convexity-meningitis with spinal meningitis. The second autopsy was on a girl of sixteen who died in the third week of the disease. In this case there was an extensive exudate over the base with effusion into the posterior fossa.

**PATHOLOGICAL ANATOMY.**—The changes in the central nervous system in cerebro-spinal meningitis have been studied, among others, by Strümpell, v. Campe, and Hagelstam. They are not always of the same kind or extent, and depend in part, at least, upon the duration of the disease. In the explosive cases the evidence of more than hyperæmia and serous exudation can often not be appreciated by the naked eye; but the microscopical examination of such cases shows that a tolerably rich emigration of leucocytes into the pia-arachnoid has already taken place. In the cases in which death has been longer delayed the inflammatory alterations are often pronounced, and they are not necessarily limited to the lepto-meninges. The substance of the brain and cord, as shown by Strümpell, are commonly involved, and the legitimacy of the terms meningo-encephalitis and meningo-myelitis has been suggested by him. While the inflammatory processes in the substance of the brain and cord are generally to be made out only with the microscope, yet in some instances, as pointed out by Zenker and Klebs, and more recently by Strümpell, abscesses of comparatively large size may exist.

In the substance of the central nervous system the invasion may take

place in three ways: (1) by direct extension from the meninges; (2) along the vessels entering from them; and (3) through the development of independent foci. These several modes were observed by Strümpell, whose observations were confirmed in our cases. Hemorrhages, especially into the substance of the cord and into the central canal, have also been observed.

The exudate in the meninges consists of pus cells, red blood-corpuscles, fibrin, and serum in varying proportions. The amount of serum may be considerable, as in the case reported by Stillé, in which three pints were present, death having taken place on the thirty-fifth day of the disease. The exudate fills the meshes of the pia-arachnoid, dips down between the convolutions, enters the ventricles of the brain and the central canal of the cord, and appears in the form of a cellular infiltration in the substance of the brain and cord. Finally, the extension of the process along their course gives rise to the symptoms referable to the involvement of the nerves.

The alterations found in other organs of the body cannot be said to be peculiar to this disease, but are such as attend infectious diseases in general. Among these may be classed the hemorrhages into the serous membranes and into the substance of certain organs; the swelling, increased granulation, and even fatty degeneration of the cells of parenchymatous organs, and the hyperæmia and degeneration of the voluntary muscles.

In our two autopsies the acute and subacute, as well as the convexity and basal forms of the disease, were represented. The first was the girl of nine, dying on the third day of the disease. Autopsy two hours after death. There were no adhesions between the dura and the skull-cap; the outer surface of the dura was smooth, the longitudinal sinus containing dark fluid blood; the dura and pia-arachnoid were not adherent; the vessels of the pia were greatly dilated and filled with blood of a dark color. The soft meninges were swollen, but no considerable quantity of fluid escaped from them; they were opaque, especially over the convexity of the brain, and in the depressions between the sulci heavy opaque white streaks and bands were visible. This exudation into the meninges was confined to the convex surface of the brain, the base being free from it, but the ventricles were somewhat dilated, and contained an excessive amount of clear serum.

The dura covering the spinal cord, especially in its inferior part, was wide and bulging. On incising it near the middle of the lumbar region about 40 c.c. of slightly turbid fluid escaped. The spinal dura was not adherent to the pia. In the meshes of the latter was an exudate which was not uniformly distributed, but was most abundant posteriorly and corresponded for the most part with the lower cervical and dorso-lumbar regions. This exudate was white and opaque and resembled that present in the brain. The vessels of the pia of the cord were likewise injected, their contents being dark in color. On section of the cord the substance presented a vivid pinkish tint.

There were subserous hemorrhages into the pleura and pericardium,



and beneath the capsule of the kidney there were punctiform hemorrhages. The cut surface of the kidneys and liver presented an opaque appearance. There was no pneumonia and the nasal sinuses were free from perceptible inflammation. The spleen was only slightly enlarged, the color was darker than normal, its substance somewhat softened, and the Malpighian bodies were swollen and strikingly distinct. The mucous membrane, especially of the small intestine, was congested, and the follicles were swollen.

The voluntary muscles were intensely red, and this was especially noticeable in those along the spine, and a large amount of blood escaped from them on incision.

The bacteriological examination of the pus in cover-slips from the exudate in the meninges of the brain and cord showed the presence there of the micrococcus lanceolatus without admixture with any other organism. The micrococci occupied pus cells and were also present in the fluid among the cells. They were fairly numerous.

Cultures were made in plain agar-agar, in glycerin-agar, and in Guarnieri's medium (Prof. Welch's modification). Owing to circumstances they could not be brought into a thermostat for forty-eight hours. Tissues were placed immediately after the autopsy in various hardening agents, Flemming's solution, bichloride of mercury, and absolute alcohol. Inoculation of animals with the exudate could not be practised at Lonaconing. The tissues were sent to the laboratory in Baltimore by express, where inoculations of mice and rabbits were made.

We had been at Lonaconing several days before a death occurred. Before our visit there had been deaths almost every day, but the mortality diminished for a while, and during those days no new cases developed. The death of the child of nine years took place at seven o'clock on the last evening we spent at Lonaconing, and the autopsy was made at nine. Cultures from the exudate were made at once on exposing it by drawing back the dura. Additional cultures were made an hour or more later. The first cultures were made at the moment the exudate was exposed, without disinfecting the surface, by inserting the needle under the raised dura; the second set, which included cultures from all the organs, was made in the usual manner after burning the surface of the organs. It is necessary to state that the second set of cultures was made in a carriage-house next a stable in which horses were kept.

On the afternoon of the day following the autopsy we left for Baltimore carrying with us fresh tissues for inoculating animals, the culture tubes, and the preserved tissues. We had proceeded as far as Cumberland, Md., when we received a telegram asking us to return to Lonaconing, as another death had occurred. The organs of the first case were, therefore, despatched by express to Baltimore, so that no unnecessary delay should occur before the inoculation of animals could be made. They reached Baltimore about noon on the following day, some forty hours after the autopsy. The animals inoculated (mice and rabbits) all

recovered. The cultures were not sent at this time, but as a precaution were kept and carried by us to Baltimore, and placed in the thermostat just fifty hours after the autopsy.

The first cultures made *at the time of the autopsy* showed a very feeble growth of diplococci, but on transplantation no further growth could be obtained. All other tubes from the brain or cord showed either no growth or an abundant one of a tolerably coarse bacillus. This bacillus is probably to be regarded as a contamination, which is believed to have gotten into the tubes at the time of the inoculation. This would not be surprising considering the disadvantageous circumstances—above noted—under which the cultures had to be made. Culture-tubes from the organs remained sterile with the exception of those from the spleen. From this a growth was obtained of pure streptococci, which formed tolerably long chains, and were devoid of pathogenic effects when introduced in large quantities into mice and rabbits.

The cultures from the second case could not be made until Baltimore was reached. The autopsy was made at 10 A.M. (twelve hours after death), and the cultures at midnight of the same day. The tubes inoculated from brain, cord, and viscera remained sterile. Plain agar, glycerin-agar, and Guarnieri were the media used. Mice and rabbits were inoculated from the exudate in the brain and cord. None succumbed.<sup>1</sup>

The histological examination of the tissues from the first case showed that an abundant exudation had taken place into the membranes of the brain and cord. It will be well, perhaps, to go more in detail into the microscopical characters of this exudate and of the lesions of the cord and brain. While the tissues were still warm they were placed, as has before been mentioned, in various hardening agents, including Fleming's solution, bichloride of mercury, and absolute alcohol.

For the study of the cellular elements in the exudate, the tissues fixed in bichloride of mercury and afterward hardened in alcohol, and those placed directly into absolute alcohol, gave the best results. The cord fixed with bichloride of mercury also showed well the alterations in the axis cylinders of the nerve roots, to be presently described. Sections from various levels were studied, and variations were noted; but they were hardly great enough to merit separate description. On the other hand, the pictures presented by the tissues prepared with  $\text{HgCl}_2$ , as contrasted with those hardened in alcohol, merit separate consideration, and we are the more disposed to treat them separately on account of the

<sup>1</sup> In view of these experiments, it may be questioned whether the organism found by us in the exudates was really the *micrococcus lanceolatus*. It is, however characteristic of the lanceolate diplococci to show a variable vitality and great variation in their pathogenic effects on animals, and from these well-established facts we are the more disposed to regard the bacteria we found as being identical with the lanceolate cocci which give rise to acute lobar pneumonia.



general significance which may attach to the variations of cell appearance depending upon hardening and staining reagents.

The cord treated with  $\text{HgCl}_2$  is well preserved, the morphological elements staining sharply. The *anterior half*: The membranes are swollen, the swelling being due to (1) the dilatation of the bloodvessels, and (2) an exudate in the meninges composed of serum and cells. The evidence of fluid is not to be made out everywhere with certainty, but areas occur in which the tissues are found pressed widely apart. The pia extending into the anterior fissure is swollen, and the bloodvessels are distended and filled with blood. This dilatation of the vessels is best seen at the anterior margin, where the fissure is widest, and again just before its termination at the white commissure, but it occurs elsewhere in the cord. The swelling of the tissues in the fissure is not due altogether to the increased accumulation of blood in the vessels and the transudation of fluid, but is in part dependent upon an increased number of cells in the tissue. These cells vary in size and possess nuclei which are of different sizes and forms. The majority of these cells have not the appearance of leucocytes with polyform nuclei—in fact but few cells having the form characteristic of these are to be seen. Moreover, in the dilated bloodvessels few polynuclear leucocytes are present. The cells which make up the increase in the tissue are chiefly small cells with round, deeply-staining nuclei and a small amount of protoplasm; the others are all of an epithelioid type. The latter are in small numbers only, and perhaps not to be regarded as essentially increased. Single red blood-corpuscles are free in the tissues and a small quantity of blood pigment is to be found deposited there. Finally, in the meshes of the membrane there are small globular masses varying in size from one-third to one-half the diameter of a red blood-corpuscle. In eosin these stain pale pink, while the red blood-corpuscles take on a bright yellowish-red color. The globular masses are less refractive than the red blood-corpuscles, which stain well; but they approach more nearly in staining and refraction shadows of red blood-corpuscles, some of which are also occasionally seen. It is not unlikely that they represent partly disintegrated red corpuscles, if indeed they are not globular masses of hæmoglobin. In the depth of the fissure the extravasation of blood is more decidedly marked than is the case near the surface.

Passing from the anterior fissure toward the anterior roots, at first a slight diminution of the cellular infiltration is noted, but at the roots the exudate is more abundant. In the angles between the roots and the cord dense accumulations of cells may be found. The forms which predominate here in the exudate are again the small round cells, although a larger proportion of cells with vesicular nuclei, some leucocytes with polymorphous nuclei, and a few red blood-corpuscles are present. This mass of cells is on the surface, and it can be seen that a proliferation of the cells of the lymph spaces has taken place in the pia beneath; in these spaces an occasional "polynuclear" leucocyte is seen. There is an almost uniform layer of cells between the anterior lateral and the posterior lateral fissures. At the posterior roots the increase in the exudate is marked. The cells fill the tissues of the membranes, and about the veins of the pia there are occasional accumulations of round cells. The polynuclear leucocytes are relatively slightly increased in

number in this portion of the cord, and are correspondingly more numerous in the bloodvessels. The predominating cells, however, resemble lymphocytes or the mononuclear cells of granulation-tissue. Toward the posterior median fissure the exudate becomes still thicker, the membranes are obscured, and more red blood corpuscles are mixed with the exudate. In this situation there are cells equal in size to four or six of the round cells; they are thin and transparent, are round or polygonal in shape, have a feebly staining protoplasm and vesicular nuclei, and often contain other cells, especially leucocytes with polymorphous nuclei, within them.

The bloodvessels of the cord itself are dilated. This is the case both in the gray and in the white matter. Just beneath the pia hemorrhages have occurred, some of which extend into the substance of the cord, and in the anterior lateral columns small hemorrhages have taken place independently of those under the pia. There is no perceptible tendency of the process of the membranes in this instance to pass into the cord. Separate foci of leucocytic accumulation do, however, occur; but they are neither large nor numerous, nor, as far as could be determined did they have any connection with bloodvessels. The largest collection observed was in size a little smaller than a miliary tubercle (Fig. 1).

FIG. 1.



Section of spinal cord showing collection of leucocytes in its ~~entrance~~ at *a*.

The ganglionic cells show certain differences among themselves, consisting of variations in the granulation of the protoplasm, the clearness of the nuclei and nucleoli (these being in some cells quite indistinct), but especially in the sharpness of the cell margins. In some, particularly in those in which the nuclei are indistinct, the margins of the cells are very indefinite. These are the only changes observed in the large multipolar cells of the anterior horns. In the posterior horns an occasional cell may be seen in which the refraction of the protoplasm is increased, and these cells are swollen and the lymph spaces surrounding them obliterated.



The changes described by Strümpell and Hagelstam in the axis-cylinders of the cord were not observed by us in these specimens, probably for the reason that, although all other parts of the cord were well preserved and stained perfectly, the axis-cylinders did not stain satisfactorily. However, in the nerve roots these as well as interstitial changes were observed, and in some instances were quite marked.

Swelling of the axis-cylinders in the cord has been noticed in nephritis, tuberculous meningitis, and leukæmia by F. Schultze, by Kohler in the oculo-motorius in tuberculous meningitis, and Hoche found it both in the cord and nerve roots in tuberculous meningitis, and describes in addition a cellular proliferation of the peri- and endoneurium of the latter. The swelling of the axis-cylinders also occurs in variola, typhoid fever and septicæmia. (Hoche.)

The anterior roots show fewer alterations than the posterior. The bloodvessels in the perineurium are swollen and a few red blood-corpuscles are found free between the nerve bundles. There is no marked proliferation in the interstitial tissue. The majority of the nerve fibres are unaltered, but still not a few are swollen and stain in hæmatoxylin feebly, those which are unchanged staining more deeply. These swollen fibres have on an average a diameter more than twice that of the others.

The normal axis-cylinders lie in a space which has apparently been formed either by the disappearance in part, or the contraction, of the myelin sheath, a faint line of myelin being still visible just inside Schwann's sheath; in some instances the myelin entirely fills the space between the axis-cylinder and the sheath of Schwann. On the other hand the swollen cylinders, which occur singly or in groups, always fill the space inside the myelin sheath, being distinguished from the latter by their larger size and by their staining properties. It is worthy of note that in those nerves in which a cellular proliferation, especially around the veins, can be made out, more axis-cylinders show this change than where the cellular increase is not so apparent.

The posterior roots show the same changes as the anterior, only in a more pronounced manner. It is not uncommon in these to find as many as twenty or thirty swollen axis-cylinders lying close together. The interstitial tissues of the nerves and the epineurium are also affected. A considerable cellular collection occurs at times in these situations, and the increase in the peri- and endoneurium reaches so high a degree as to obscure the nerve fibres. This, however, seldom happens. The cells forming the collections are principally of the type of small round cells.

Specimens of the cord hardened in absolute alcohol were found well suited for the study of the cellular elements making up the exudate. Sections stained in aqueous solution of fuchsin or magenta show, as the important difference between them and those of the tissues hardened in solutions of bichloride of mercury, that more polynuclear leucocytes are present in the exudate than was before apparent. These cells are found on the anterior but in larger numbers on the posterior aspect of the cord, and in the cell masses in the latter, leucocytes presenting the most irregular nuclear forms are met with. Nuclear fragments are to be found in small quantity. Notwithstanding this difference, the cell-forms which are usually regarded as being derived from the fixed cells are still present in large numbers. In one section a small collection of

polynuclear leucocytes, not associated with a bloodvessel, was found in the lateral horn. Again, in a section of one of the anterior roots a small collection of polynuclear leucocytes, and near by an evident proliferation of the nuclei of Schwann's sheath, was observed. Single polynuclear leucocytes are found between the nerve fibres, and in the bloodvessels there is an evident leucocytosis.

Specimens taken from various parts of the brain were hardened in the same way as the cord. The tissues from bichloride and absolute alcohol again gave very good preparations. Various staining reagents were employed—hæmatoxylin and eosin, fuchsin, magenta. For the study of the bacteria, the methods of Gram and Weigert were used, as well as solutions of methylene-blue and gentian-violet applied in the ordinary way.

The thickness of the exudate is not only less on the convexity than in the sulci, but it is not uniform over the convolutions themselves. In some places the exudate over the convolutions is two or three times as deep as in other places. But it is in the sulci (Fig. 2) that the greatest accumulations of cells have taken place. The characters of the exudate are not essentially different from those described in the cord, but the relative number of the different kinds of cells is not the same. There is dilatation of the bloodvessels of the pia, and an increase of leucocytes with polymorphous nuclei in these vessels is more common than in those of the cord. Hemorrhages are also found, amounting at times to considerable extravasations and at others to the escape of a few corpuscles only. A very little golden-yellow pigment is seen now and then. In the section the pia is lifted up from its connections with the underlying brain substance in many places, although the brain substance beneath is intact.

The cells composing the exudate consist of polynuclear leucocytes in considerable, perhaps predominating, numbers, but many other cells are also present. Among these latter are cells of the type of lymphoid cells, larger cells with vesicular nuclei, and, finally, cells much larger than either of these, which in certain situations are so numerous as to make up a considerable part of the exudate. These cells, as indicated, are not uniformly distributed. They may be found on the convexity, but are more common in the sulci. In size they equal several of the ordinary cells with vesicular nuclei, and they themselves possess nuclei of this type. They are either circular or polygonal in outline, thin and translucent, and what especially characterizes them is the fact that they often contain enclosed in their protoplasm other cells, principally polynuclear leucocytes. The number of cells which are included varies. Sometimes only two or three are seen, but as many as fifteen have been counted in one cell. Besides the leucocytes small round cells and red blood-corpuscles may be enclosed in these larger cells. (Fig. 3.) As stated, these large cells have vesicular nuclei and abundant protoplasm, and present the appearances of epithelioid cells. While regarding them as proliferated endothelium derived from the pia, we can offer no explanation of the purpose which they serve in taking up other cells. The cells which they contain are practically normal; they possess nuclei which stain well and are of normal appearance. On the other hand, the large cells themselves are apparently normal. Sometimes it happens that the nucleus of one of the large cells is not sharply defined, or that the cell protoplasm stains in eosin a little more deeply than is usual with endothelium.



FIG. 2.



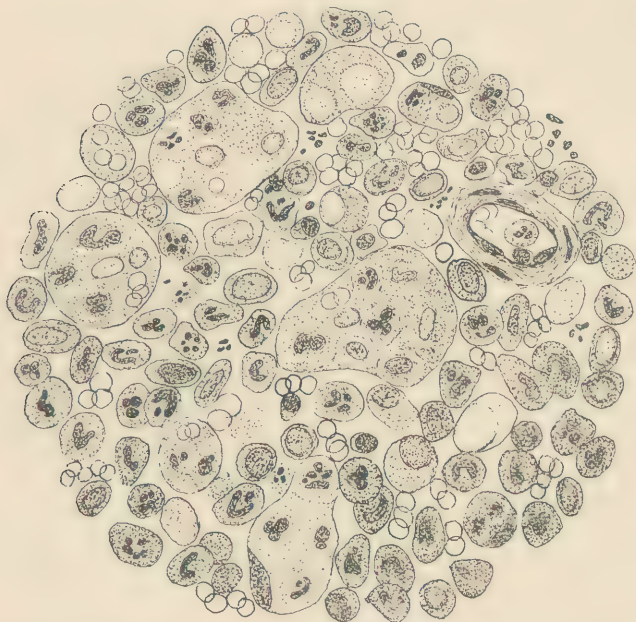
Section of the brain from Case I., showing dilatation of bloodvessels and the relative amount of exudation on the surface and in the sulcus.





In the brain, besides inconsiderable hemorrhages, the cellular infiltration of the meninges has advanced to a slight extent into the substance along the vessels, and a few scattered leucocytes without vascular connection can be made out. In addition there is slight cedema, as indicated by the rarefied appearance of the cortex. Fibrin plays a very small part in the exudate, sections of the tissue hardened in alcohol stained by Weigert's method showing only a small amount.

FIG. 3.



From the exudate in the meninges in Case I. Polyform leucocytes, endothelioid cells, red blood-corpuscles, and the larger cells with inclusions. A few cells with fragmented nuclei, and free nuclear fragments, also present.

Cover-slip preparations made at the time of the autopsy from the exudate in the brain and cord showed a fair number of diplococci, usually lancet-shaped and always surrounded by capsules, and, as previously stated, they were sometimes free and sometimes enclosed in cells. The results of our attempts to cultivate the organisms, as well as the inoculations of animals, have already been mentioned. In the tissues stained for bacteria by the methods of Gram and Weigert, as well as with gentian-violet and methylene-blue, typical diplococci were found. They were not particularly numerous, but were present there to the exclusion of other organisms, so far as could be determined by these staining methods.

The changes in the other organs may be summed up in a few words. In the *kidney* the bloodvessels generally are dilated, and small hemorrhages have occurred into the tubules. The tubes containing blood preserve their epithelium, but this is compressed. The epithelial cells of the convoluted tubes are swollen and granular, and here and there

contain fine fat-droplets. An occasional epithelial cell devoid of a nucleus is seen. The *spleen* is congested and the lymphatic tissue of the nodules increased in amount.

The second case was that of a girl of sixteen who died in the third week of the disease. The autopsy was made twelve hours after death.

The dura was strongly adherent to the skull-cap, and on removing it about 200 c.cm. of slightly turbid fluid containing white flakes escaped from the posterior fossa. The longitudinal sinus and the veins over the convex surface of the brain were distended with dark fluid blood, and the arteries were prominent. The fluid in the pia over the cortex, which was increased in amount, was turbid. On the base, covering the pons and the upper half of the medulla, was a firm white deposit which was intimately adherent to the underlying tissues. Over the base, from the pons to the optic chiasm inclusive, there was in the pia a fluid, milk-white in color, which was especially abundant in the anterior perforated space and over the optic commissure. The fourth ventricle and the lateral ventricles contained greenish-yellow gelatinous pus—indeed the former was completely filled with it. Both the lateral ventricles were dilated, and the choroid plexuses covered with an opaque exudate. A similar opaque exudate extended along the sheath of the auditory nerve into the bony canal.

The pia-arachnoid, throughout the entire length of the cord on the posterior surface, contained a gelatinous exudate fully two millimetres in thickness, the exudate on the anterior surface being less marked.

The *kidneys* were swollen, cloudy, and cyanosed. The *liver* was cloudy and of very flabby consistence. The *spleen* was somewhat swollen, softened, and deep reddish-brown in color, the Malpighian bodies being very distinct. The mucous membrane of the *intestines* was swollen throughout, congested, and its lymphatic apparatus was hypertrophied. There was no pneumonia.

From the pus in the ventricles and from the exudate over the base of the brain, the micrococcus lanceolatus was obtained on cover-slips. The organisms were present in much smaller numbers than in the previous case. In the other organs no bacteria were found. The results of cultures and inoculation of animals from this individual have already been mentioned.

The tissues from this case were hardened in the same manner as those from the previous one, although they were not obtained in so fresh a condition. This fact is evident from the preservation, especially of the the cord. The exudate in the meninges stains well, while the substance of the cord does not stain satisfactorily. As in the previous case, the largest accumulation of cells on the anterior aspect of the cord is at the fissure, and the two points of greatest accumulation are on the surface and in the depth of the fissure. Laterally the exudate is not uniform, but is gathered into foci, and is more abundant where the anterior roots are given off. At this place the exudate passes along the roots as they leave the cord. The exudate becomes thicker still over the posterior aspect of the cord, but it is not uniform. The section has been carried through the dura, and where no mechanical separation has taken place the exudate is found to be in contact with this membrane.



The thickness of the exudate over the posterior is several times that over the anterior aspect of the cord, and where the posterior roots come off the exudate surrounds them.

The cells which compose this exudate are again recognized as round cells, larger cells with vesicular nuclei (these varying in size, and often including other cells in their substance), and polynuclear leucocytes. There are fewer of the large cells present than in the sections of the brain from the acute case. The polynuclear leucocytes do not predominate in number over the other cells. In addition to the cells on the posterior aspect of the cord, where the exudate is thicker, it contains a material which stains very deeply in hæmatoxylin, and has an amorphous appearance. In this mass cell-forms can still be made out at times, but they do not stain. Nuclear fragments are also seen. This amorphous material may reach a considerable amount, and it is doubtless derived from the softening and disintegration of the exudate.

The pia is thickened in places by an actual new growth of connective tissue. This thickening is next to the cord, and is represented by foci of young and cellular connective tissue; in some of these there are already well-developed fibres with intercellular substance.

The nerve roots are not unaffected. Surrounding the veins are collections of round cells and the number of cells in the perineurium of the nerve bundles and in the epineurium is much increased. This cellular proliferation is sometimes so extensive that it must have offered some interference to the functions of the nerve by the pressure exerted. The cellular proliferation in the nerve may actually obscure the nerve fibres. The fibres themselves show changes similar to those already described in the acute case. Following the vessels as they enter the cord, a cellular proliferation is often seen about them.

The meninges of the brain show in general the same condition as those of the cord. Sections made from various parts of the base covered with exudate show the latter to be composed of the same elements. Where the exudate is thickest the amorphous layer staining deeply in hæmatoxylin is also most pronounced. The pia is thickened by a new growth of tissue as well as by the exudate contained within its meshes. This new tissue is young, and where it occurs the pia is intimately adherent to the brain tissue. The vessels which pass in from the pia often show a proliferation of round cells in the perivascular lymph spaces, and such vessels may be followed for a considerable distance into the brain substance, the largest aggregations of these cells being seen in the neighborhood of the lateral ventricles. Here they reach a considerable size, are always associated with vessels, and are composed almost entirely of small round mononuclear cells, although a few polynuclear leucocytes may be seen among them. The lateral ventricles were, as previously stated, filled with pus. The epithelium of the ependyma is only in part preserved, and where it is deficient, cells with nuclei of a vesicular type forming a layer two or three cells thick are seen. In the pus adhering in the section to the ependyma, many fragmented nuclei exist. A single calcified area the size of a millet-seed was observed.

Sections of the brain and cord stained by Weigert's method showed fibrin to be absent. In sections the diplococci lanceolati were found, but only in small numbers.

The liver shows small collections of leucocytes (polynuclear) in the neighborhood of the portal spaces. The spleen is congested, and hem-

orrhages have taken place into the parenchyma. There is, in addition, a general hyperplasia of the lymphatic apparatus. A few "red blood-corpuscle-carrying cells" are to be seen, and many of these contain blood pigment as well.

#### SYMPTOMATOLOGY.

Regarding the symptomatology, we shall content ourselves with giving a very brief *résumé* of the notes taken, paying most attention to the symptoms most prominent in this epidemic. We shall lay especial stress upon certain of the clinical features (*e. g.*, the blood examination) which heretofore have been insufficiently studied. The peculiar conditions which obtain in an infectious intra-cranial disease are such as to render the clinical picture very complex. In local infections elsewhere in the body (*e. g.*, pneumonia, diphtheria) it is comparatively easy to separate clinically the symptoms and physical signs due to the local action of the infectious agent on the one hand from those dependent for their origin on the absorption and distant action of its toxic products. In diseases within the skull, however, more than anywhere else in the body, it is the size of the pathological new production and the quickness of its development which are of significance for the severity and course of the disease. Quinke has recently again emphasized the fact that even the simple serous accumulations within the skull-cavity, no matter where they are situated, if sufficiently extensive, may produce the most severe symptoms, or even cause death.

In epidemic cerebro-spinal meningitis we have to think of the results which may follow, not only the more or less sudden outpouring of an exudate (cortical, basal, or intra-ventricular), but also those which are consequent upon the direct and remote action of the toxins which are produced by the micro-organisms, and we have to decide whether the lesions in distant organs (lungs, heart, joints) are to be looked upon as absorption-effects or as a localization of the same organism in these parts, or as complicating infections due to other bacteria. As Leyden has pointed out, the gravity lies more often in the evil effects of the exudation on the functions of the brain than in the severity of the infection; if the meningitis be cortical, epileptiform convulsions endanger life; if there be marked exudation into the ventricles, then coma and brain paralysis too often ensue.

From what we have said, and from the results of pathological examinations, the complexity of the question becomes easily evident, and an attempt to analyze the different disturbances in function, and to connect each definitely with its pathological basis would seem at first to be well nigh hopeless. Nevertheless, with the constant acquisition of facts and better methods of technique, we need not despair of finally arriving at a position in which we shall be able to cope more or less successfully with these problems.



It was possible at Lonaconing to make out most of the different types of the affection which have been described—fulminating, acute, subacute, intermittent, and abortive. The onset of the disease was, in the majority of the cases, sudden, the individual being attacked without warning with severe headache and vomiting, symptoms which were often followed in a few hours by delirium, stiffness and retraction of the neck, and severe constitutional disturbances. In only a few cases was there a definite recognizable prodromal stage, with general malaise, headache, and dragging pains in the limbs.

Compared with other epidemics, the number of fulminating cases (*cas foudroyants*) was large, no less than ten patients dying within forty-eight hours after seizure, one child indeed succumbing in eight and another in ten hours after the appearance of the first symptoms. In the less violent but still severe cases the symptoms lasted from six to fourteen days, when either death occurred or signs of slow improvement ensued. Many abortive cases were observed in which, after a sudden onset, with perhaps severe symptoms, the patients recovered with striking rapidity.

Several cases of the "intermittent type" occurred during this epidemic, and in these periods of comparative well-being alternated with marked exacerbations. The convalescence was often tedious, and the danger was by no means over when the acute symptoms had subsided. Even after there was good reason to believe that the causative bacteria were all dead and convalescence seemed to be established, serious symptoms would reappear, which would suggest that as long as the exudate is not completely reabsorbed there is danger.

The symptoms in general, we may say, presented no regularity. The disease is full of surprises, and the clinical phenomena of one day or hour may differ greatly from those of the next.

Especially inconstant was the course of the fever, and the temperature charts are interesting, chiefly in that they show that no fixed type of pyrexia can be definitely assigned to this disease. Nor did the height of the fever bear any relation to the severity of the other symptoms; the sudden and often marked elevations and depressions of the temperature independent of general symptoms could be explained only by assuming a direct interference with the functions of the thermo-regulatory centres. Even the absence of pyrexia did not permit the making of a favorable prognosis.

The other symptoms referable to disturbances of the central nervous system, the headache, the vertigo, the delirium, the paralysis of the eye-muscles, the deafness, the general hyperæsthesia, and the twitchings showed almost as great irregularity as did the temperature curve.

Among the clinical appearances noted which were due to lesions of the cranial nerves and their centres in the different cases may be mentioned anosmia, strabismus (almost always divergent), nystagmus (usually hori-

zontal or vertical), inequality of pupils, photophobia, ptosis, defects of vision, facial rigidity, trismus, slowed respiration, Cheyne-Stokes breathing, deafness and disturbances of speech.

On account of its rarity, it is interesting to record one case in which we observed definite rotary nystagmus. The patient was a girl of seventeen, who had severe general symptoms with distinct evidence of a basal exudate. During a part of one day the left eyeball was rotated definitely in its socket, the excursions apparently corresponding to the limits of the movements of rotation. On reviewing the literature, we have been able to find reference to only one similar instance—a case mentioned by Jaffé.

The intra ocular changes have been especially studied in this epidemic by Dr. R. L. Randolph. Out of thirty-five cases in which he examined the fundus, it was normal only in seven. The most frequent alteration was passive congestion in the retinal veins, with congestion of the optic disks. In several cases there was a distinct optic neuritis, and in one instance the central vein was thrombosed.

The retraction of the neck was very commonly present; in some cases the occiput was drawn well back between the scapulæ. The thighs and legs were frequently flexed, but extreme opisthotonos was not often seen. There was general hyperæsthesia of the skin, and attempts to change the position of a patient gave rise to severe pain. In the graver cases there were marked twitchings of the muscles and tendons, and in some, especially a short time before death, convulsions and coma.

The tendon reflexes varied much, but in many cases were diminished, which is to be attributed, no doubt, to the extent of the interference with the posterior roots of the spinal nerves.

Beyond the nervous arrhythmia, the respiratory organs were not markedly implicated, and it was only rarely that one met with an associated bronchitis or broncho-pneumonia. General cyanosis was not uncommon. A very frequent feature in the epidemic was epistaxis, a symptom which does not seem to have often attracted the attention of observers elsewhere.

The pulse was sometimes slowed, sometimes accelerated, and often intermittent. Beyond the blowing systolic murmurs so frequently heard over the cardiac area in children in febrile affections, there were very few symptoms referable to the heart or pericardium.

The lips, teeth, and tongue were covered with sordes, especially in the graver and more protracted cases. A few patients showed mild anginas, and the tonsillar crypts were not infrequently filled with white cheesy-looking plugs. The chief symptom pertaining to the digestive system was the vomiting, which, in some cases, was persistent and intractable, leading to inanition and emaciation. Where the retraction of the neck was great there was often difficulty in swallowing; in some cases the



dysphagia appeared to be due to interference with the normal innervation. The bowels were, as a rule, constipated, although diarrhoea occasionally occurred. Indeed, in four cases a well-marked dysentery was observed, the feces containing mucus, pus, and blood. Occasionally in a grave case there would be incontinence both of the urine and the feces.

In one case of dysentery the feces were carefully examined. The reaction was found to be alkaline, the odor very foul, and mucus, pus, and blood were visible to the naked eye. A fresh specimen of the mucopurulent portion, examined microscopically, showed, besides the epithelium from the surface of the mucous membrane, many round cells of variable size, which were often fatty and vacuolated. Some of these were certainly polynuclear leucocytes, others resembled rather lymphoid cells. In the protoplasm of several cells which had the size of polynuclear leucocytes, besides large vacuoles, one could make out single included cells of small size. Red blood-corpuscles were also present. Smear cover-glass preparations, dried and stained in various ways, showed as the predominating organism lancet-shaped cocci in pairs, apparently encapsulated. In addition, there were slender bacilli, a few shorter, thicker bacilli (resembling *B. coli communis*), and short chains of streptococci. It must be mentioned that in the two cases which came to autopsy large lumbricoid worms were found in the alimentary canal, and, on inquiry, we learned that they had been observed in many of the cases, both in the vomit and in the feces.

The spleen was at times slightly enlarged, as shown by percussion; the splenic dulness, however, did not pass beyond the costo-articular line, and in no instance was the border of this organ palpated. Abdominal retraction was not a prominent symptom on the whole. The only symptom referable to the liver was the occurrence of mild jaundice in two of the cases.

The cutaneous changes were widely divergent. Many of the cases ran their course without any apparent exanthem, and if one were to be guided only by the majority of cases in this epidemic he would be compelled to discard the name "spotted fever" for the disease. Herpes was very common, and formed an early and important symptom. It was situated chiefly on the lips, nose, ears, and neck following the distribution of the cutaneous vessels and nerves. Purpuric and petechial eruptions were seen in a comparatively small proportion of the patients; one of the commonest forms of eruptions was an indistinct purplish mottling over the surface of the body, which appeared and disappeared almost under the eyes.

The urine varied in amount in different cases and in different stages of the disease. As a rule it was concentrated, but occasionally a patient would pass large quantities having a low specific gravity. In the severer

cases, and especially in those running an acute course with high fever, slight albuminuria was common, and microscopical examination of the sediment showed the presence of hyaline and granular casts. Ehrlich's diazo-reaction was negative in every case in which it was applied. The reaction has, however, been present in the urine in a few instances in meningitis, but only according to Ehrlich in very severe cases. The urine contained an excess of phosphates, a point to which several observers, notably v. Grimm, have called attention. In many cases there was a white precipitate of triple phosphates equal to one third or more of the volume of urine passed. In none of the specimens examined could the presence of sugar be demonstrated.

THE JOINTS.—Nearly twenty per cent. of the severe cases suffered from complicating joint affections, the knees being most frequently attacked, the elbows, wrist, and ankle following in frequency in the order named. The effusions were peri-articular as well as intra-articular, and the joints were swollen and reddened, resembling closely those of acute articular rheumatism. Indeed, there were cases which, had it not been for certain initial symptoms indicating a meningeal process, could easily have been diagnosed as nothing more than attacks of rheumatism. Similar cases have been noted in other epidemics, and there are references in the literature which draw attention to the prevalence of meningitis and of rheumatism in the same community at the same time.<sup>1</sup>

Speaking generally, it may be said that for this epidemic at least, complications in the joints occurred more frequently in the better class of patients, and it is interesting to note that the meningeal symptoms appeared to be favorably influenced by their appearance.

Kernig, of St. Petersburg, has described a symptom which he believes to be pathognomonic of meningitis. In thirteen cases he observed a peculiar flexion-contracture (*Beuge-kontraktur*) of the knee-joints which

<sup>1</sup> These facts are, we think, not without importance as bearing upon the etiology of acute rheumatism. There can be little doubt, it seems to us, although for the proof we must look to cultural experiments, that in the joint complications in epidemic meningitis, the articular and the peri-articular inflammations are due to local infections with the same bacterium which has set up the meningitis. Moreover, in at least one case of genuine acute rheumatism the micrococcus lanceolatus has been isolated in pure culture from the joint effusion, and Foa and Bordoni-Uffreduzzi have been able to set up a polyarthritis in rabbits by subcutaneous inoculation of this diplococcus. The frequent association of rheumatism with endocarditis, and with inflammation of the pleura, pericardium, and peritoneum lend support to the view that at any rate in a certain proportion of the cases the pneumococcus may be the cause. Nevertheless it is probable that acute articular rheumatism will, ere long, be proven to have no *etiological unity*, just as has already been proven for the inflammations of the serous membranes generally. It seems probable that the entrance of pyogenic organisms of different varieties into the circulation, under circumstances which are inconsistent with the development of the phenomena of a general septicæmia, may give rise to inflammations in some one or more of the serous membranes of the body—be it meninges, pleuræ, pericardium, peritoneum, or joint surface, the particular ones attacked depending on certain peculiarities either in the virulence of the invading organism or in the lessened resistance at the moment of the serous membrane implicated.



could not be reduced when the patient was in the sitting position. In attempting to extend the knee, the leg could not be straightened further than a point where it made an angle of about  $135^{\circ}$  with the thigh, although when lying or standing this contracture was completely absent. If the patient lay on his side with the thighs drawn up the symptom was still present. It has been claimed that the same phenomena may be seen in many other conditions (old age, chronic alcoholism, etc.), but Kernig asserts that he has examined thousands of individuals with particular reference to this point, and has never found this contracture except in cases of meningitis. Unfortunately we were not familiar with this suggestion when at Lonaconing, and so cannot say anything as to the value of "Kernig's symptom."

**THE CONDITION OF THE BLOOD.**—There have been very few opportunities for studying the blood in cases of epidemic cerebro-spinal meningitis since the more general employment of the finer methods of hæmatological technique; and in the literature we have been able to find only meagre references to the subject by Halla, v. Limbeck, and Rieder. The two former found a leucocytosis in cases of suppurative meningitis, while Rieder observed two cases of epidemic cerebro-spinal meningitis, one having 20,100 white corpuscles, the other 17,500 to the cubic millimetre. We were fortunately able to examine the blood of several of the cases at Lonaconing, but shall include in this report only a few typical examples.

In order to avoid error, every precaution was taken in these examinations. The blood in all cases was taken with the aid of a sterile lancet from the lobule of the ear, previously thoroughly cleansed with alcohol and ether. The blood was examined fresh in each case, care being taken to secure specimens which spread out into a layer of only one corpuscle in thickness. These were examined immediately with an oil immersion lens. The hæmoglobin was estimated by the instrument of v. Fleischl. The readings were made in a dark room, with artificial light, and through a cylinder of paper some twelve inches in length. Moreover, the readings were made by two individuals, and where the results differed at all the mean of the readings was recorded. By this method of control any gross error was avoided. For the enumeration of the corpuscles the blood-counter of Thoma-Zeiss was employed, the methyl-violet solution of Toison being used as a diluting fluid. Finally coverslips were prepared for drying and staining by the methods of Ehrlich. For this purpose particular care was taken to secure good specimens, and on subsequent examination all imperfect preparations were discarded. We shall epitomize the results of our examinations. In the fresh blood slide no marked variations in size or shape of the red corpuscles could be made out; in some of the cases, however, there was distinct pallor of the red cells. The increase in the number of the leucocytes was quite evident in many cases in the examination of the fresh drop of blood, and a greater number of white corpuscles appeared to be motile than one sees under normal conditions. Many of the leucocytes presented a striking vacuolation, a condition which, we believe,

is not uncommon in the leucocytes dependent on other causes. The blood-platelets were present in clumps, but did not appear to be decidedly increased or diminished in numbers.

As to the number of corpuscles present, the average of a number of counts shows that a diminution of the red cells is not a marked feature of the disease. In some of the advanced cases, with emaciation there was a moderate oligocythæmia, but in the majority of instances the full complement of red blood-corpuscles was present. The hæmoglobin, however, in all cases examined was somewhat diminished in amount, so that the individual corpuscular holding in hæmoglobin (*valeur globulaire*) was below par. A well-marked leucocytosis is, we believe, a constant phenomenon in the disease during its active stages. In no case examined, except in convalescent patients, was it absent. The number of white corpuscles varied in different cases in our experience, between 12,000 and 32,000 to the cubic millimetre. That the degree of variance is greater, however, there can be little doubt, and it is probable that further investigations will prove that still larger leucocytoses may exist, especially in cases of meningitis associated with complications in the lungs or joints. The dried specimens were fixed by heating for an hour and a half on a copper bar at 120° C., and then stained, some of them in solutions of eosin and methylene-blue, some in the triple stain of methylene-green, acid fuchsin and orange green.

In none of these specimens were micro-organisms found, although they were patiently looked for. The "color analysis" of the leucocytes showed in every case the increased number of white blood-corpuscles to be due to an increase in the cells with neutrophilic granules and polymorphous nuclei. The mononuclear cells (small and large) were relatively diminished in number. It will be seen that these changes in the blood are not peculiar to meningitis, but are quite in accord with the leucocytoses associated with suppurative inflammations, or inflammations accompanied by well-marked local exudation anywhere in the body.

As examples the following four cases may be cited :

Bessie B. (Case XVII. of Dr. Porter's series), aged four years, always healthy before; had been a bright, stout, well-nourished girl. One evening in the last week in January felt cold and chilly, and had distinct rigor during the night, followed by vomiting and severe pain in the head. During first week she was very restless, had muscular hyperæsthesia, inequality of pupils, rapid pulse, and uttered a sharp cry from time to time. Two purpuric spots appeared on buttocks. Retraction of the neck began about the eighth day. Up to this time the patient ate and drank well, and appeared rational. The mother now noted that the child could not use the right arm, and on examination it was found rigid and swollen. Herpetic eruption appeared about the tenth day.

*Note dictated February 14:* Child lies on left side, moderately emaciated, legs drawn up, thighs flexed, right arm rigid, resists movement; head retracted; whole body held stiff and rigid; attempts to move the child cause her to cry out; face slightly mottled and has a bluish tint; lips bluish-red and covered with sordes; remains of herpetiform eruption visible. Tongue grayish-yellow, moist coating thicker in the centre than at the edges; pupils even, midway between contraction and dilatation. No ocular paralyses; veins in forehead rather prominent; thorax symmetrical; expansion equal; marked pulsation in vessels of neck; resonance clear throughout front,



axillæ, and back; a few whistling rhonchi heard at bases. Pulse equal at the two wrists, 18 to the quarter, very irregular and arrhythmical. Sometimes there would be two or three beats of varying intensity followed by a pause corresponding to the time of from two to four beats; volume of pulse rather small. Apex beat of heart in fourth interspace 1 cm. inside the left nipple line. Dulness not increased; loud blowing systolic murmur heard over whole cardiac area, greatest intensity at the third left interspace 1 cm. from sternal margin. Pulmonic second sound relatively accentuated. Splenic dulness begins at the eighth rib and extends to the costal margin; does not pass the costo-articular line. Border not palpable, possibly owing to rigidity of abdomen. Liver dulness begins at the seventh rib in right mamillary line and extends to costal margin; border not palpable. Skin dry, no œdema; no marked change in tendon reflexes; no lymphatic enlargement.

The blood examination was made on February 14. Even in the fresh drop of blood the increase in the white elements could easily be made out. The count showed 4,448,000 red and 24,000 white blood-corpuscles; hæmoglobin, 72 per cent. Dried and stained preparations showed a marked increase in the number of polynuclear leucocytes with  $\epsilon$ -granules, and a relative diminution in the number of lymphocytes and large mononuclear leucocytes.

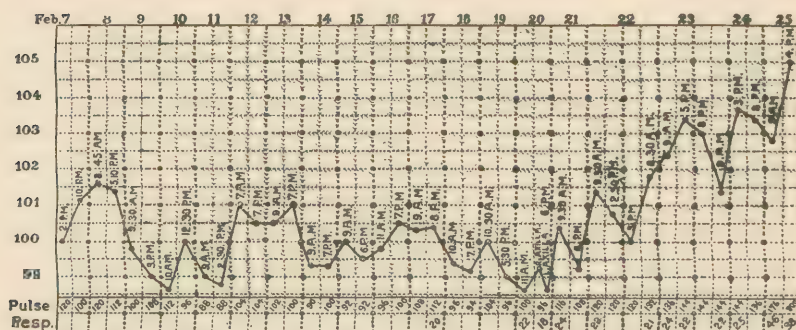
Florence D., aged sixteen years. The onset in this case had been gradual, the patient having pain in the head and back for several days before any serious symptoms appeared. On January 29, at 1 P.M., she had a severe chill followed by excruciating pain in the head, causing loud shrieks and restlessness; this was associated with vomiting and excitement. Next day the patient was decidedly deaf and more or less stupid. Later she became delirious, and often had to be held in bed. She picked her nose from time to time and had several attacks of epistaxis. Distinct purpuric eruption appeared on face and neck and a few spots on body. None of them were very bright and none of them turned yellow or green afterward. During part of her illness she had retention of urine and had to be catheterized. Her bowels were constipated. Spleen and liver not distinctly enlarged. The temperature never went higher than 103.5°. She had marked eye symptoms, including divergent squint, paralysis of accommodation, and nystagmus. On ophthalmoscopic examination there was a definite optic neuritis in the right eye (Dr. Randolph). The girl died at the end of the third week of the disease. Toward the end she was much cyanosed and showed well-marked Cheyne-Stokes respiration. Her urine was examined several times and found to contain a trace of albumin and numerous hyaline and granular casts.

The blood was examined on two successive days in the third week. As the results of the two examinations were practically the same, we give that made on February 15. In the fresh blood slide, the examination of two or three fields sufficed to show that the leucocytes were distinctly increased in number. The vacuolation of the leucocytes was especially striking in this case. Hæmoglobin (v. Fleischl), 45 per cent. Blood-count: red blood-corpuscles, 4,896,000; white blood corpuscles, 24,500. The dried and stained specimens showed a marked relative increase (over 85 per cent.) in the neutrophils with polymorphous nuclei, and a relative decrease in the different mononuclear forms. Several typical normoblasts seen.

Agnes S., aged nine years, taken ill on February 7, 1893. Complaining of chill, severe pain in the head, and vomiting. The temperature, as will be seen by referring to the accompanying chart, was not high at the

beginning. There was severe pain in the neck and inability to move muscles of limbs on account of pain. No marked retraction of neck. She continued with comparatively mild symptoms for some ten days when, on February 17, she had diarrhoea, cramp-like pains in the abdomen, with a little blood and mucus in the stools. These symptoms were relieved the next day, but on the 18th she suffered from extreme pain in left ear, requiring morphine for its relief. On the 20th it was noticed that she had no power in right arm and leg, and there was some incontinence of urine and feces. Paralysis of right side of face. On 23d temperature rose to 101.8°. Next day well-marked evidence of complicating bronchitis and broncho-pneumonia. Pulse and respiration became more rapid and temperature higher. Death on evening of February 25. Temperature, 105°; pulse estimated at over 200.

FIG. 4.



The blood examination in this case was made on February 14th. In the fresh blood slide the increase in the white elements was easily demonstrable. Marked vacuolation of the leucocytes. Hæmoglobin (von Fleischl) 72 per cent. Blood-count, red blood-corpuscles 5,032,000; white corpuscles 29,500. Cover-glass preparations from this case dried and stained in the "triple stain," gave the following "differential count" of white elements:

		Proportions in normal blood.	
		Per cent.	Per cent.
Small mononuclear	53	4.9	15 to 25
Large mononuclear and transition forms	74	6.8	4 to 6
Neutrophils with polymorphous nuclei	946	87.3	70 to 75
Eosinophiles	0	0.0	1 to 5
Myelocytes	10	1.0	
Total number counted	1093	100.0	

Only one nucleated red blood-corpuscle (typical normoblast) seen in the whole slide.

In making the differential counts it was thought best to adopt the simple classification given above rather than the more complicated one of Uskow. According to the suggestion of Thayer, we have made the counts so that the small mononuclear elements correspond to the small and large lymphocytes, the small transparent forms and some of the smaller transitional forms of Uskow; the large mononuclear and transition forms including all other non-granulated forms, with the exception of transparent polynuclear leucocytes. In terms of Uskow's classification the characteristic change in these leucocytoses consists of an increase



in the *ripe*, and especially in the *over-ripe* elements with a relative decrease in the number of the *young* or *unripe* elements.

The complete absence of leucocytes with eosinophilic granules did not hold for the other cases examined. The number of typical myelocytes seen in this case was rather striking, and, had the patient been an adult, would perhaps have been of considerable pathological significance. In the blood of children, however, one often sees, even under normal conditions, a variable number (nearly always, however, under 1 per cent.) of these cells.

For comparison, we give the results of a differential color analysis of the blood taken from a woman, thirty-eight years of age, who had suffered from a prolonged attack of meningitis, and had a moderate leucocytosis:

	Per cent.
Small mononuclear elements . . . . .	10.9
Large mononuclear and transition forms . . . . .	2.1
Eosinophiles . . . . .	0.6
Neutrophiles with polymorphous nuclei . . . . .	86.4
Myelocytes . . . . .	0.0
	<hr/> 100.0

Lizzie L., aged fifteen years (service of Dr. Skilling), was seen during convalescence. She had suffered from a severe attack, the temperature at the beginning reaching nearly 105°. There had been retraction of the neck and delirium for some four or five days, and excessive vomiting. Abundant herpatic eruption on lips, cheeks, hands, and wrists, the discoloration still remained. Marked constipation at first. No paralysis, no joint complications, no tenderness below neck. Had been sitting up the day before blood examination was made.

In the fresh blood-slide the red corpuscles were noticed to be distinctly paler than normal. No apparent increase in number of white elements. Hæmoglobin 55 per cent. Red blood-corpuscles, 5,004,000. White blood corpuscles, 9000. In the dried and stained specimens the different varieties of leucocytes were present in about normal proportions, the over-ripe (multinuclear) elements being still, however, slightly in excess. A few typical normoblasts seen. This count is given in that it shows the disappearance of the leucocytosis with the advent of convalescence.

TABLE.

Patient.	Age.	Attending physician.	Day of disease.	Temperature at time of examination.	Hæmoglobin (v. Fleischl).	Red blood-corpuscles to c.mm.	Value of globule.	White blood-corpuscles to c.mm.	W. R.	Remarks.
					p. ct.					
B. B.	4	Dr. Porter	17th	...	74	4,448,000	0.84	24,000	1 : 185	Dysentery as a complication.
F. D.	16	Dr. Porter	18th	101.2°	45	4,896,000	0.47	24,500	1 : 199	Albumin and casts in urine.
A. S.	9	Dr. Porter	7th	100.5	72	5,032,000	0.7	29,500	1 : 170	
L. L.	15	Dr. Skilling	...	99.2	55	5,004,000	0.55	9,000	1 : 556	Convalescent.

A word of explanation is necessary with regard to the low percentage of hæmoglobin found in the blood of Florence D. and Lizzie L. Both these girls showed clinically a decided pallor of the skin and mucous mem-

branes, although as the blood-counts show the red corpuscles were present in nearly normal numbers. The marked diminution in the *valeur globulaire*, taken with the age and sex of the patients, made us think of a pre-existing chlorosis, and on inquiry we learned that both had been noticed to be slightly pale for some months previous, and that both had complained of more or less constipation and certain menstrual irregularities. It is almost certain, therefore, that the low percentage of hæmoglobin observed in these two cases was not entirely dependent upon the meningeal inflammation.

And finally, in this connection, it will not be out of place, in view of the many interesting observations which have been made regarding the bearing of the presence or absence of a leucocytosis in diseases due to the lanceolate diplococci (acute lobar pneumonia, pneumococcus-infections in rabbits) upon the severity of a given infection and upon the prognosis, to state that, in the fatal cases which we have had the opportunity of examining during life the presence of a leucocytosis was always demonstrable. While for confirmation of this point it will be necessary to study many more cases in future epidemics, yet the evidence, as far as it goes, is in favor of the view which we have already mentioned, that death in cerebro-spinal meningitis results from the local intra-cranial mischief, rather than from the infection *per se*.

The death-rate at Lonaconing corresponded to that of an epidemic of moderate severity, about 40 per cent. of the cases (excluding those classed as abortive) proving fatal. Hirsch, in his monograph, states that out of 15,632 cases 37 per cent. died. v. Ziemssen placed the mortality of mild epidemics at 20 per cent., and of the severest epidemics at 70 per cent.

#### PATHOGENESIS.

The disease, then, being known to be due, at least in the majority of instances, to the action of a specific micro-organism, viz., the micrococcus lanceolatus, we have next to consider by what mode the infectious agent gains entrance to the body, and more particularly into the meninges of the brain and cord, and in what way, if at all, it is thrown off. Again we have to inquire whether, if it can be thrown off, it will ever ~~then~~ *again* be in a condition to infect other individuals.

Unfortunately a wholly satisfactory answer cannot at this time be given to these questions. We are not yet in possession of sufficient data based on a close study of the epidemiology and bacteriology of the disease, to enable us to more than indicate the probable mode of infection and the conditions which predispose to the origin and propagation of the disease.

The simultaneous prevalence of other infectious diseases in the localities in which epidemic cerebro-spinal meningitis existed, has been held to be of some significance. The occurrence of pneumonia at such times must be regarded as of special importance, for, as we have said, the same infectious agent is the cause of both diseases, and in the epidemic of



cerebro-spinal meningitis studied by Foà and Bordoni-Uffreduzzi the most of the cases were complicated by pneumonia. Epidemic parotitis has been noted as occurring in a community in connection with or just before the outbreak of this disease. Parotitis was epidemic at Lonaconing at the time of the prevalence of meningitis, and we may remark that there are in the literature references which go to show that the micrococcus lanceolatus may be the cause of this disease also.

Again, other infectious diseases, scarlet fever, measles, typhoid fever, influenza, and coryza, have been mentioned by different writers as concomitant epidemics.

While in pneumonia, and probably a certain number of cases of parotitis and coryza, the same organism as that found in meningitis is known to occur, yet in the other infectious diseases mentioned, the infectious agent, so far at least as is known at present, is in none of them the micrococcus lanceolatus. Moreover, it is to be remembered that meningitis does not attack by preference those suffering or just recovering from other infectious diseases, if we exclude pneumonia. These diseases occur as concomitants or as precursors only.

Hence it is clear that in the search for predisposing factors we must look further than the infectious diseases with which epidemic meningitis may coexist. And it is not improbable that we shall find that, although one disease does not depend upon the other for its development, yet the same conditions of life which permit one to flourish may also engender the other.

It has been suggested by Strümpell that there may be some relation between coryza and epidemic meningitis. This, he thinks probable, on account of the observations of Weigert, that in some cases of the disease there is a purulent inflammation of the nasal sinuses. Weichselbaum found in some of his cases of meningitis purulent inflammation of the nasal and sphenoidal sinuses and the middle ear, and in all these he demonstrated diplococci. One must, we think, hesitate before accepting it as even highly probable that the majority of cases originate in this way. On the other hand, a sharp line of distinction must be drawn between those cases which are definitely primary and those which are secondary. There are, undoubtedly, cases in which there has been an extension of disease in the middle ear to the meninges, and why should not the same thing happen in diseases of the nasal sinuses? Such cases may simulate the sporadic form of the disease. But what is necessary is to see whether or not cases associated with diseases of the middle ear and those of the nasal mucous membrane occur in such numbers during an epidemic as to make this mode of origin the probable one in all. In the acute case in which we performed an autopsy no disease of the nasal sinuses existed.

With our present knowledge it seems more probable that we have to

do with an infection by the way of the blood current rather than by continuity from the nose or ear. The common occurrence of meningitis in pneumonia indicates the possibility as well as the frequency of this mode of infection. In those cases in which pneumonia does not occur, other sources of entrance for the infectious agent must be sought; and to this category belongs especially the epidemic form. In any consideration of this subject at the present time, infection from the nasal<sup>1</sup> and oral cavities, in the latter case by lymphatic communication, as suggested by Ortmann, is a possibility which cannot safely be rejected. Nevertheless, the writers have been led to believe that the intestinal tract may be regarded as the way of entrance into the blood-current, if not in all, at least in many of the cases.

In two of the cases which we observed clinically, and which afterward proved fatal, there was dysentery. Cultures and cover-slip preparations were made from the evacuations of one of these, and the predominating organism present was the micrococcus lanceolatus. In both of the cases which came to autopsy there was enteritis. And in other epidemics the occurrence of dysentery has been noted. Yet constipation as a feature of the disease is of more common occurrence than diarrhœa. This may be considered at first as militating against the conception of the intestinal tract as the place of entrance into the body of the infectious agent. But it is perfectly conceivable that the organisms may enter through the intestinal canal without first producing a demonstrable lesion therein, and find in the meninges of the central nervous system a *locus minoris resistentiæ*. The case of meningitis, as reported by Ortmann as due to the micrococcus lanceolatus secondary to typhoid fever is important as indicating the possibility of entrance from the intestine. Here, however, undoubted lesions of the mucous membrane were present.

Owing to the slight vitality of the organism in acid media, and as the intestine must become invaded after the infectious material has first passed through the stomach, it is necessary to draw attention to one point that may be of significance. Whether in all the persons attacked there is an alteration in the gastric juice by which its acidity is either diminished or altogether abolished, we cannot say, as we were unable to obtain the contents of the stomach from a number of cases. But in the vomit obtained from one child sick of the disease, free hydrochloric acid was demonstrated to be absent. Still, were this not the rule, there are periods in health during the fasting hours, when the stomach is free, or nearly so, from acid contents. In this connection the observations of Ewald are full of interest. He found that when water was introduced into the stomach a small amount passed immediately into the intestine; after about an hour the rest went suddenly over into the duodenum, and this

<sup>1</sup> The lymphatics of the mucous membrane of the nose can be injected from the sub-arachnoidal lymph space (Schwalbe, Key, and Retzius.)



part had no acid reaction, so that any bacteria present were not subjected to the harmful influence of an acid medium. Flügge has recently emphasized this point when dealing with the method of spread of cholera through drinking-water. In our disease the diplococci are of course not necessarily in the water imbibed, but in the process of swallowing it is easy to understand how they could be washed from the mouth and throat (their constant habitat), and so gain entrance to the stomach, and finally to the intestines uninjured.

The importance of considering the intestine as a probable infection-atrrium in epidemic cerebro-spinal meningitis becomes evident when it is remembered that about 80 per cent., and according to some authors (Kruse and Pansini) 100 per cent., of all persons in health carry about constantly in their mouths the micrococcus lanceolatus, and according to Netter, in 20 per cent. of these the organisms possess sufficient virulence to kill animals when injected into them. This fact removes the necessity of searching for the infectious agent outside the body, in, for example, the soil or the water.

Most writers on the subject now agree that the disease is not contagious, but is rather of "miasmatic" origin. The localization of the infectious agent in the closed cavity of the central nervous system certainly does not favor the infection of the surroundings. Still in some epidemics, that in Hamburg for example, the disease was known to appear in a locality in which it previously existed, but from which it had disappeared; and the interval of time which had elapsed was in some instances considerable. These facts would seem at first to be irreconcilable with the view that there is no infection of locality. We have shown that an organism possessing the culture and morphological properties of the micrococcus lanceolatus is thrown off with the dejections in some cases of cerebro-spinal meningitis, and as indicated by the experiments of Bordoni-Uffreduzzi, Guarnieri, Netter, Patella, Nikiforoff, Sirena, and Alessi, and Kruse and Pansini, the organisms may retain their vitality and even virulence when dried in sputum, blood, etc., sometimes for four months. Hence we are not at this time justified in excluding the possibility of the infection of locality. This assumption seems, however, in view of the wide distribution of the organism in nature, to be hardly necessary. It is, we think, more probable, that the local conditions which enabled the first cases to appear, persisting, other susceptible individuals are attacked, so that fresh cases appear in the site of the previous ones, in fact that we have to do with a "predisposition of community" rather than an "infection of locality."

If we are then to believe that the disease is, in the majority of instances, the result of an auto-infection, and this would be equally true whether we conceive it to be due to the entrance of the bacteria from the nose or pharynx or from the intestinal canal, it still remains for us to determine

the nature of the unusual conditions which render the system vulnerable to the invasion of the micro-organism, and what it is that brings about the localization by preference of the morbid process in the cerebro-spinal meninges.

When excluding air, water, soil and food, as carriers of the infectious agent, we by no means intend to deny that they may play an important rôle in the causation of the disease. And concerning Lonaconing, the local conditions are such as would naturally produce a lessening of the powers of resistance of a number of individuals, and thus render them, although apparently in good health, susceptible to the disease. While in this epidemic, as we have already said, the more prosperous classes were by no means exempt, it was chiefly the poor that suffered, and the disease prevailed particularly in localities in which the houses were close together, and in which overcrowding existed, with the attendant evils of unsanitary arrangements, improper and insufficient food, and unclean bedding and clothing.

Nevertheless, although the facts pointed to a predisposition of the whole community outside the merely personal predisposition, in the end the resistance of the tissues of each individual must necessarily be of prime importance in determining infection or immunity.

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